The Journal of HEREDITY

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Fetal Death Through Blood Incompatibilities

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Childlessness—Voluntary or Involuntary

A Timetable of Mouse Embryogeny

The Inheritance of Red Hair

Twins and Super-Twins

Mathematics and Growth Forms

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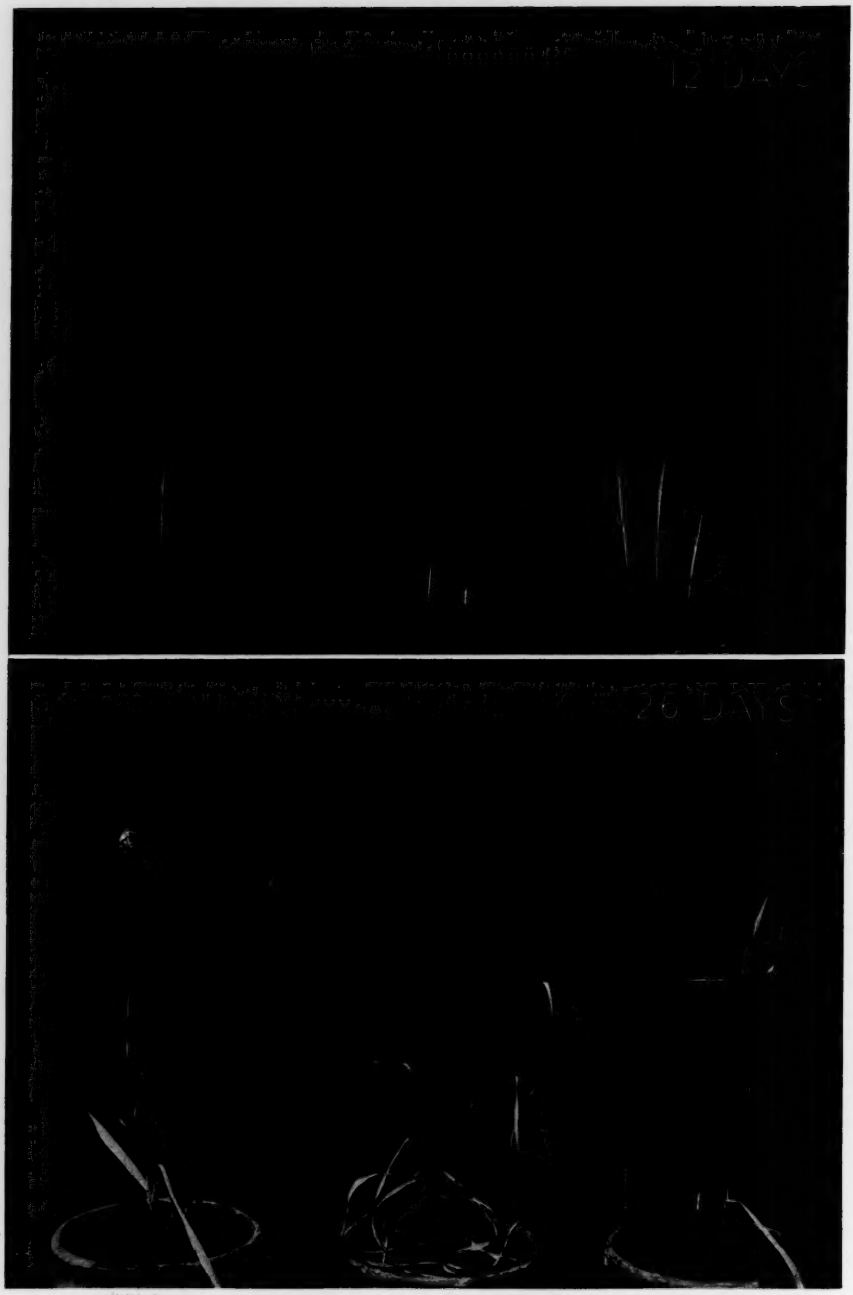

Trumbull **Trumbull × Marquillo F_1** **Marquillo**

NECROSIS OF HYBRIDS DUE TO COMPLEMENTARY GENES

A—Three plants of each of the two wheat varieties Trumbull and Marquillo and their F_1 hybrid, at 12 days when necrosis of the tips of the first leaf of each hybrid became distinct. *B*—The same plants at 26 days, showing the stunting of the hybrids and the progress of the necrosis in the second and third leaves and the appearance of small but as yet non-necrotic fourth leaves. The hybrid plants were dead on the 39th day.

COMPLEMENTARY LETHAL GENES IN WHEAT

Causing a Progressive Lethal Necrosis of Seedlings*

RALPH M. CALDWELL† AND L. E. COMPTON‡

CROSSES of certain soft red winter wheat varieties (*Triticum vulgare*) with the spring wheat, Marquillo (*T. vulgare*), have resulted in the production of F_1 seedlings which die within a period of approximately four to six weeks following seeding (Figure 1). F_1's of crosses of other wheats with Marquillo have shown no abnormalities. The F_1 plants, destined to die in the early seedling stage, emerge and apparently develop normally until the two-leaf stage has been reached. Then the first leaf begins to wither and dry, first at the tip, and then progressively on to its base. As the first leaf entirely collapses, the same process is initiated successively at the tips of the second, third, and fourth leaves, the latter failing to grow to normal size. The embryonic stem tip and leaf primordia apparently succumb from lack of organic nutrition, since new leaves are produced until food sources are exhausted. The necrosis is associated with a certain degree of maturity of the leaf tissue, as evidenced by its delay until the two-leaf stage of growth, and its initiation in the leaf tips which represent the oldest tissue of each leaf. The condition here described has been designated as progressive lethal necrosis, to differentiate it from other types of heritable necrosis of wheat plant tissue wherein necrosis, while extensive, may not necessarily be lethal.[3] The crossed kernels containing the embryos of the necrotic seedlings appear normal. The roots of the necrotic seedlings have been carefully observed and appear not to become necrotic. The leaves are normal green and the rate of growth prior to the onset of necrosis equals that of the parents. (See Figure 1.) Crosses of the Marquillo variety with the unnamed *vulgare* strains, F.H. 27 and H.H. 55 have resulted in normal F_1 plants.

Results similar to those obtained with Marquillo were produced when a durum wheat (*T. durum*, P.I. 94587) of Portuguese origin, was crossed with some of the same varieties. A third wheat, Big Club (C.I. 11761) (*T. vulgare compactum*) was reported verbally to the writers by Dr. G. A. Wiebe to give nonviable F_1 seedlings when crossed with the variety Dawson (*T. vulgare*). Seed of this strain of Big Club was furnished by Dr. Wiebe, to enable us to compare its behavior, as a parent in crosses, with that of Marquillo and the durum, P.I. 94587. It has been found to give results identical with those from these varieties so far as lethal necrosis in its F_1's is concerned. A preliminary note on some of these results has been published.[1] Painter, et al.,[4] have noted the lethality of F_1's of certain crosses involving Marquillo.

The necrotic or normal behavior of the F_1 seedlings of the crosses mentioned above is shown in Table I. It will be noted that Marquillo, durum (P.I. 94587), and Big Club produced necrotic F_1's in those cases wherein they were crossed with Wabash, Trumbull, Minhardi, and Dawson, and normal F_1's if crossed with H.H. 55 and F.H. 27 or

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intercrossed among themselves. Trumbull and Wabash also produced normal F_1's when intercrossed or crossed with H.H. 55. Reciprocal crosses gave similar results, and therefore are not distinguished in Table I. In a few instances necrotic or normal F_1 plants occurred as exceptions from a cross giving otherwise exclusively normal or exclusively necrotic F_1's. These probably resulted from mutation or outcrossing in the parent varieties or from selfing due to imperfect emasculation.

The explanation of these results suggests a genetic hypothesis involving complementary dominant genes, one of which is possessed in common by Marquillo, durum (P.I. 94587), and Big Club; and the other by Trumbull, Wabash, Minhardi, Dawson, and F.H. 16. The strains H.H. 55 and F.H. 27, upon this hypothesis, must be recessive for both these factors. The hypothesis was tested by crossing the varieties of each of these groups, carrying one postulated gene complement, with the double recessive varieties, H.H. 55 and F.H. 27; and testcrossing the resultant F_1's with varieties carrying the other postulated gene complement. If lethality were controlled by two dominant genes such testcross populations would show segregations of half necrotic and half normal seedlings. The data from these tests, reported in Table II, support this hypothesis, since none of the ratios depart significantly from the expected and the chi-square test indicates the homogeneity of the data presented for the different crosses. The ratio of the total of 315 normal to 321 necrotic plants is extremely close to the expected 1:1.

Intercrosses of surviving plants from these two groups of testcrosses, each representing a heterozygote of one of the two complementary lethal genes, were made and the progenies grown. These progenies would be expected to segregate in a ratio of three normal to one necrotic if lethality were controlled as postulated. The results, presented in Table III, show fairly close agreement to this ratio, none of the deviations being significant.

Tests of the allelic nature of the one complement of lethal genes in Wabash and Trumbull and of the other complement in Marquillo and Big Club were made by crossing the F_1 Wabash $\times$ Trumbull, to Marquillo and the F_1 Marquillo $\times$ Big Club to Wabash and to F.H. 16. Two of these crosses produced 62 plants all of which were necrotic, while in the Big Club-Marquillo $\times$ F.H. 16 cross, one normal plant appeared in a total of 28 (Table IV). Had the genes been nonallelic and nonlinked, three necrotic plants to one normal would have been expected. The deviation from the expected on the basis of a 3:1 ratio is highly significant, the exceptional normal plant probably resulting from impurity of parental stocks or imperfect emasculation. It is assumed therefore that the gene for lethality contributed by Marquillo is identical with that from Big Club and that the gene from Wabash is identical with that from Trumbull.

Discussion

The name progressive lethal necrosis may seem redundant when first encountered. However, necrosis is common among wheats and frequently results in premature death of much leaf tissue, but not, so far as we know, in an unnatural death of the plant.[3] A severe form of such a heritable, nonlethal necrosis of leaves and stems is associated with the false "black chaff" so common among stem-rust resistant progenies of crosses between Hope wheat (C.I. 8178) and varieties of *T. vulgare*. Hence, the progressive necrosis dealt with here is distinguished by the term *lethal*.

Apparently the embryonic stem tip and leaf primoridia of the necrotic wheat plant are unaffected, at any rate not until death is imminent from failure of the necrotic leaves to supply necessary food materials, or of the older stem tissue to transport them. The necrosis is expressed only after leaf tissue reaches a certain physiologic maturity. The first leaf remains normal until reaching maximum size and a second leaf is well grown; then necrosis sets in at its tip,

which represents the oldest chlorenchymatous, foliar tissue of the plant. In connection with vernalization experiments the potentially necrotic F_1 plants were grown in a refrigerator for 60 days at a temperature of about 3°C. These plants grew as did normal seedlings in the ice box, reaching a height of two to three inches. Such plants would have died within five to six weeks under greenhouse conditions. When transplanted to the greenhouse, after the 60-day cold treatment, the plants produced normal chlorophyll and developed to the two-leaf stage parallel with normal plants. Then the symptoms of progressive necrosis appeared as usual at this growth stage. The inhibition of maturation by low temperatures or darkness apparently prevents the development or action of the cause of necrosis in the leaf tissues of plants bearing the lethal genetic constitution.

As far as known to the writers one of the genes of this complementary pair is known only in Marquillo (*T. vulgare*), a 42-chromosome type; Big Club (*T. vulgare compactum*), a 42-chromosome type, and P.I. 94587 (*T. durum*), a 28-chromosome type. It is of interest to note that Marquillo resulted from a cross between the *vulgare*, Marquis spring wheat, and the durum, Iumillo. Search for this gene has not been extensive and likely its presense would be revealed elsewhere. The other dominant gene of the complementary pair occurs, as reported above, in Trumbull (C.I. 5657), Wabash (C.I. 11384), Minhardi (C.I. 5149), Dawson (C.I. 3342), and F.H. 16; and in addition, as indicated by their lethal combinations with Marquillo, in American Banner (C.I. 6943), Honor (C.I. 6161), Michigan Amber (C.I. 5620), Nittany (C.I. 6962), Poole (C.I. 3488), Purdue No. 1 (C.I. 11380), and Rudy (C.I. 5656). The recessive alleles of both of the dominant lethal genes were found to occur in Kawvale (C.I. 8180), Leap (C.I. 6958), Purkof (C.I. 8381), and Minturki (C.I. 6155) in addition to the strains H.H. 55, C.I. 11682, and F.H. *27* involved in these genetic studies.

Two lines of Marquillo, derived by single plant selection, produced some normal F_1 plants in crosses where only necrotic F_1's were to be expected. Apparently some of the plants of these lines lacked the lethal gene complement of Marquillo. These lines were characterized as typical Marquillo lines in the field. This heterogeneity may have arisen from chromosomal aberration, to which Marquillo is subject as shown by Powers.[5]

The symbol *Le* is proposed to designate the one complementary dominant gene occurring in Marquillo, Big Club, and P.I. 94587; and *Le2* for the other complementary gene occurring in Trumbull, Wabash, and the several other varieties. The genotype of the varieties of the Marquillo group would therefore be *Le Le le2 le2*; that of varieties of the Trumbull-Wabash group *le le Le2 Le2*. The F_1's resulting from crosses between

TABLE I. Survival of F_1 hybrids of certain wheat crosses.

Variety*	C. I. No.†	Marquillo C.I. 6887		Durum P.I. 94587		Big Club C.I. 11701		Trumbull C.I.5657		Wabash C.I. 11384	
		number surviving	total	number surviving	total	number surviving	total	number surviving	total	number surviving	total
Marquillo	6887			69	70	2	2	0	32	0	32
Trumbull	5657	0	32	—	—	0	11			20	20
Wabash	11384	0	22	0	19	0	14	20	20		
Minhardi	5149	0	32	1	10	—	—	—	—	39	39
Dawson	3342	—	—‡	0	7	0	22	—	—	—	—
F.H.16		0	9	—	—	—	—	—	—	—	—
F.H.27		41	41	34	34	12	12	6	6	—	—
H.H.55	11682	61	62	21	21	14	14	12	12	10	10

*F.H. 16 and F.H. 27 are unnamed selections from the cross Turtle (C.I. 11512) X Hungarian (C.I. 4836-11); H.H. 55 is an unnamed selection from the cross Hope (C.I. 8178) X Iumar (C.I. 6462).

†C.I. refers to accession number of the Division of Cereal Crops and Diseases, Bureau of Plant Industry, U. S. Department of Agriculture.
P.I. refers to Introduction number of the Division of Plant Exploration and Introduction, Bureau of Plant Industry, U. S. Department of Agriculture.

‡Indicates that the cross was not observed.

TABLE II. Segregation of necrotic and non-necrotic plants in testcrosses involving complementary factors for progressive lethal necrosis.

	Number of seed sown	Number of Plants Emerged	Normal	Necrotic	X^2*	P
(Marquillo-F.H.27) X Trumbull	60	58	28	30	0.07	>0.7
(Trumbull-F.H.27) X Marquillo	172	149	61	88	0.29	>0.5
(F.H.27-Marquillo) X Wabash	79	76	41	35	0.47	>0.3
(F.H.27-Wabash) X Marquillo	53	53	28	25	0.17	>0.5
(Trumbull-H.H.55) X Marquillo and reciprocal	104	103	45	58	1.04	>0.2
(Marquillo-H.H.55) X Trumbull	8	7	4	3	0	>0.9
(Marquillo-H.H.55 X Wabash	53	52	32	21	3.28	>0.1
(H.H.55-Wabash) X Marquillo and reciprocal	82	79	35	44	1.02	>0.3
(H55-Big Club) X Wabash	15	14	8	6	0.07	>0.7
(F.H.27-Big Club) X Wabash	26	24	13	11	0.04	>0.8
Total	652	636	315	321		
X^2 of totals = .056; P(d.f.=1)						>.90
Total X^2 of different crosses= 6.06; P(d.f.=10)						>.90

*Calculated from an expected ratio of 1:1, normal to necrotic.

TABLE III. Segregation of necrotic and non-necrotic plants resulting from crosses of surviving testcross progenies, heterozygous for complementary factors for progressive lethal necrosis.

	Number of Plants Emerged	Normal	Necrotic	X^2*	P
[(Trumbull-F.H.27) Marquillo]X [(Marquillo-F.H.27) Trumbull]	97	77	20	1.00	> 0.3
[H.H.55-Wabash) Marquillo] X [Marquillo-H.H.55) Wabash] and reciprocal	64	54	10	3.00	> 0.08
[Trumbull-F.H.16) Marquillo] X [Marquillo-H.H.55) Wabash]	26	17	9	.82	> 0.30
Total	187	148	39		
X^2 of totals=1.71; P (d.f.=1)>.10 Total X^2 of different crosses 4.82; P(d.f.=2)>.10					

*Calculated from an expected ratio of 3:1 normal to necrotic.

TABLE IV. Tests of the allelic nature of each complementary gene for lethal necrosis in different wheats.

	Number of seed sown	Number of Plants Emerged	Normal	Necrotic	Number expected Normal	necrotic
(Wabash-Trumbull) X Marquillo	25	25	0	25	0	25
Marquillo X (Wabash-Trumbull)	17	17	0	17	0	17
(Big Club-Marquillo)X Wabash	20	20	0	20	0	20
(Big Club-Marquillo) X F.H.16	28	27	1	26	0	27

varieties of the two groups, and possessing the genotype *Le le Le2 le2,* have invariably died and thus prevented the direct study of the segregation of these genes in advanced generations.

Kostyuchenko[1] has reported a case of premature death of F_1 seedlings of certain crosses which may occur at the third leaf stage, or may be delayed to later growth stages, dependent on environmental conditions and the parentage of the crosses. In certain cases the F_1's matured to produce the F_2 generation which segregated in approximately a 9:7 ratio of nonviable to viable plants. He concluded that complementary factors were responsible for the premature dying. Apparently the type of lethality we are dealing with differs from that reported by Kostyuchenko, particularly in the constancy of lethality. In our studies the necrotic F_1's invariably died in the early seedling stages, whether grown in the field or greenhouse or during different seasons. McMillan[3] has reported a "firing" of wheat leaves at the flowering stage of growth presumed to be controlled by three complimentary factor pairs one of each being dominant in the "firing" plants. The leaves were affected as a whole and not basipetally from the tip. The condition was not lethal. A case of lethality in barley seedlings resulting from the interaction of two complementary factors, reported by Wiebe,[6] differs from this case in wheat, in that the barley seedlings usually failed to emerge from the soil.

Summary

A *progressive lethal necrosis* of F_1 wheat seedlings, resulting from certain crosses, has been shown to be controlled by a pair of complementary factors. The appearance of the necrosis is delayed until the two-leaf stage, when it is initiated in the tip of the oldest leaf and progressively involves the entire first, second and third leaves and an abortive fourth leaf, soon after which the seedling invariably dies.

Two vulgare wheats, Marquillo (C.I. 6887), and Big Club (C.I. 11761), and a durum wheat (P.I. 94587), were shown to possess in common one of the dominant gene complements designated as *Le Le,* while the other dominant complement, designated as *Le2 Le2,* was found more commonly, occurring in the vulgare varieties Trumbull (C.I. 5657), Wabash (C.I. 11384), Minhardi (C.I. 5149), Dawson (C.I. 3342), and others. A number of vulgare varieties including H.H. 55, F.H. 27, Gladden, Purkof, and Leap were found to be recessive for both of these genes and therefore crossable with varieties of either the Marquillo or Trumbull genotype.

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◆

Artificial Mouse Subspecies

H. D. Goodale (*Amer. Nat., 76* (1942), No. 766, pp. 515-519) describes progress made in the development of four stocks of mice with different amounts of white. All were descended from five foundation animals. One stock was characterized by a few white hairs and continued by random breeding. In another stock the few white hairs were eliminated. The third and fourth stocks were selected for total white, but no progress seemed to have been made for the appearance of white in exact locations. Under wild conditions these stocks might constitute new species or subspecies.—*Expt. Sta. Record.*

SEROLOGICAL FACTORS AS POSSIBLE CAUSES IN SPONTANEOUS ABORTIONS*

PHILIP LEVINE†

Division of Laboratories, Newark Beth Israel Hospital

RECENT discoveries regarding the interaction of certain of the inherited blood differences have given a new realization of the dangers of isoimmunization reactions between mother and fetus. One dominantly inherited agglutinable factor of the red blood cells—the so-called "*Rh* factor"—has been shown to be responsible for a specific disease of the newborn, and evidence is accumulating that this factor, and possibly interactions between other incompatible blood types in mother and fetus, may be a cause of repeated abortions and of stillbirths in apparently normal women. It is too soon to assay the full implications of these developments in genetics and the pathology of inherited blood incompatibilities, but enough is known to suggest very strongly that they are possibly a factor in the causation of abortions, stillbirths, and perhaps certain other morbid conditions of the neonatal period. In this article it is proposed to summarize present knowledge concerning the part played by this Rhesus factor in causing anemia of the newborn (erythroblastosis fetalis) and to present evidence that the *A* and the *B* blood group factors may also interact disastrously to fetal development.

The first observations were made in connection with the origin of atypical agglutinins which were held responsible for serious intra-group transfusion accidents in pregnant women.[28, 24] Further investigation yielded proof that isoimmunization of the mother was the essential feature in the pathogenesis of a specific familial disease of the fetus and of the new-born infant, i.e. erythroblastosis fetalis.[26] Clinically it was already known that mothers of erythroblastotic infants have a higher than normal incidence of spontaneous abortion. Although the causation of erythroblastosis fetalis was unknown at the time, it was suspected that the same mechanism could also operate in the early fetal period. [4, 29]

As will be shown below, a particular blood factor, designated the "Rhesus factor" or "*Rh* factor," because it was discovered in the Rhesus monkey, plays the villain's role in this recurring tragedy. This *Rh* factor, common to the blood of the Rhesus monkey (*Macacus mulatta*) and to the blood of 85 per cent of human beings, has been shown to be responsible for inducing isoimmunization of the non-*Rh* mother against *Rh* fetal blood. In 90 per cent of the cases of erythroblastosis fetalis the mother's blood is not agglutinated by anti-*Rh* serum, i.e., the mother's blood is *Rh*-negative (*Rh*—). This value is to be contrasted with an incidence of 15 per cent *Rh*— in the general population. In this large group of *Rh*— women, 100 per cent of the fathers and affected infants are *Rh*+. It is assumed that enough of the *Rh*+ blood of the fetus finds its way into the *Rh*— maternal circulation to stimulate the mother to produce anti-*Rh* agglutinins. These agglutinins then pass the placental barrier so that their continual reaction with susceptible *Rh*+ fetal blood results in the intra-uterine hemolytic process which is so characteristic of the pathologic and clinical features of the three recognized forms of erythroblastosis fetalis, i.e., fetal hydrops, icterus gravis and anemia of the newborn.

From this brief description one may

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conclude that the pathogenesis of erythroblastosis fetalis is to be classified primarily under the heading of genetic and constitutional causation. It is significant that in the great majority of mothers who have borne erythroblastotic infants, the prenatal period, and the delivery, are entirely uneventful except in the much smaller fetal hydrops group. Among these there is an incidence, in about 30 per cent of the cases, of toxic symptoms in the mother.[7,13] Granted that the specific *Rh* factor in fetal blood may immunize the mother with resulting pathologic effects on the fetus or infant, the question naturally arises: why may not isoimmunization brought about by other fetal blood factors also terminate in morbid conditions of the fetus and the new-born? This issue is pertinent because so little is known about the large group of early and late fetal deaths, especially in view of the great individuality of human blood resulting from the permutations and combinations of several well described hereditary blood factors aside from *Rh*, such as *A* and *B*, *M*, *N*, *P* and still others.

Evidence of a preliminary nature will be presented below, showing that the factors *A* and *B* in fetal erythrocytes may actually immunize mothers who lack these factors, and that this actually may result in abortions and stillbirths. In comparison with the clear-cut relationship of the *Rh* factor and erythroblastosis fetalis, the evidence that factors *A* and *B* do cause abortions and stillbirths through isoimmunization is not as convincing. However, the statistical proof for the pathogenesis of erythroblastosis fetalis is so thoroughly established that it serves indirectly to support to a considerable degree the concept of isoimmunization by *A*, *B*, or other factors. Furthermore, the general procedure for obtaining proof of fetal and neonatal morbidity by isoimmunization by other blood factors does not differ in principle from that found so effective in the *Rh* studies on erythroblastosis fetalis. For these reasons erythroblastosis fetalis assumes an importance far greater than its low incidence would seem to justify. Hence a complete description of the developments leading to the concept of isoimmunization by the *Rh* factor will be presented.

Isoimmunization by the Fetus: The *Rh* Factor

Isoimmunization implies immunization within the species. Obviously, this phenomenon cannot occur unless individual differences in cellular or tissue components exist within the species. As is generally known, the four blood groups *O*, *A*, *B* and *AB* serve as an excellent example of intra-species differentiation in red blood cells. Until recently, isoimmunization in man was observed quite rarely and only in cases of intra-group transfusion reactions following repeated transfusions. In these cases it was assumed that the atypical agglutinins causing the reaction resulted from the repeated transfusion of donor's blood which contained antigenic (immunizing) blood factors which were foreign to the recipient. Puzzling exceptions to this situation were the severe and sometimes fatal intra-group transfusion reactions associated with pregnancy, in which a violent reaction followed the very first transfusion. That isoimmunization had occurred was evident from the demonstration of atypical agglutinins in the recipient's blood, which were held responsible for the transfusion reaction. Consequently, Levine and Stetson[28] assumed that the source of the isoimmunization was a blood factor in the fetus which was foreign to the blood of the mother.

Curiously enough, the specificity of the atypical agglutinins in the mother was almost identical with that of the anti-Rhesus blood immune serum prepared experimentally by Landsteiner and Wiener.[17] Consequently, the terms *Rh* and anti-*Rh* were employed respectively for the antigenic blood factor in the fetal blood and its agglutinin in the mother's serum.[24,26] The significant observation was made that the pregnant women who suffered from transfusion accidents because of immunization by the *Rh* factor in fetal blood, had obstetrical histories characterized by

a high incidence of abortions, stillbirths and neonatal deaths. It was apparent that the two phenomena—isoimmunization and fetal-death—were correlated.[24]

The nature of this relation became clear since the cause of fetal and neonatal death in a smaller number of the early cases could be attributed, on the basis of clinical and pathological grounds, to erythroblastosis fetalis. Accordingly, it was assumed that this condition is brought about by (1) isoimmunization of the *Rh*— mother by the *Rh*+ fetal blood and (2) the passage of maternal immune agglutinins through the placenta and their continuous reaction with the susceptible fetal blood. The other characteristic feature of erythroblastosis fetalis, i.e., familial incidence in certain matings, and a sporadic appearance in others, can be explained on the basis of homozygous and heterozygous character of the *Rh* factor in the father's blood.[22]

The statistical proof supporting these concepts is presented in Table II.

Another element in the proof is the demonstration of anti-*Rh* agglutinins in mothers of affected infants. It is evident that the chances for demonstrating these antibodies are better if the tests are carried out soon after delivery.

It is of great importance for the prevention of maternal mortality in this group to understand that the *Rh*— mothers of erythroblastotic infants who have no agglutinins in their serum nevertheless have been immunized as evidenced by the occasional occurrence of severe transfusion shock following the transfusion of *Rh*+ blood. It cannot be too strongly emphasized that all *Rh*— patients be transfused with blood of *Rh*— donors.[19]

Without going into the details of the serologic tests it may be stated that not all human anti-*Rh* sera derived from mothers of erythroblastotic infants give identical specificities.[22] In addition to that type of serum giving 85 per cent *Rh*+ reactions there is one variety giving 87 per cent and a third one giving about 70 per cent positive reactions. For the diagnosis of erythroblastosis fetalis and for the prevention of intra-group transfusion accidents either the 85 per cent or the 87 per cent serum will be satisfactory.*

In the 10 per cent of the cases in which the mother is *Rh*+, or both parents are *Rh*—, it is assumed that other agglutinable factors such as *Hr, A, B* or perhaps still other unknown factors

TABLE I. Outcome of 37 Pregnancies in 7 Patients.

Mothers	*No.*
Anti-Rh agglutinins	6
Transfused	5
Transfusion shock	5
Death after transfusion (anuria)	3

Births	*No.*
Normal babies	10
Erythroblastosis Neonatal death Stillbirth	15
Abortion or miscarriage	10
No data	2

TABLE II. Statistical Proof.

Blood Studies of	*Percentage of Rh factor*	*Incidence*
	+	−
Random sample of U. S. population	85	15
350 mothers of affected infants	10	90
204 husbands of Rh— mothers	100	0
139 affected infants of Rh— mothers	100	0

In the Rh+ mothers, isoimmunization may be induced by *Hr, A, B,* or other unknown factors in fetal blood.

TABLE III. Incidence of anti-Rh agglutinins in Rh— mothers of erythoblastotic infants.

When tested	*Incidence— Per Cent*
Up to 2 months postpartum	47
2 months to 1 year	25
1 year or longer	5

*It is of interest that anti-*Rh* sera giving 87 per cent reactions contain several agglutinins so that after absorption with selected bloods the absorption fluids behave like the 85 per cent or the 73 per cent sera respectively. This effect could not be produced with the serum giving 85 per cent reactions. In agreement with Landsteiner and Wiener these three varieties of human anti-*Rh* sera are identified as follows[20]: 87 per cent reactions, anti-$Rh_{1\text{-}2}$; 85 per cent reactions, anti-Rh_1, and 73 per cent reactions, anti-Rh_2.

of fetal blood may immunize the mother. The factor *Hr* demonstrable by means of an agglutinin in an *Rh*+ mother is related genetically to the *Rh* factor, probably in the form of an allelomorph.[23]

Heredity of Erythroblastosis Fetalis

As indicated above, there are two strikingly contrasting obstetrical histories given by mothers of erythroblastotic infants. In certain instances only the first one or two children may be normal while all subsequent pregnancies terminate either in abortion, stillbirth, or in one of the three recognized forms of erythroblastosis fetalis. In other matings, only one of numerous pregnancies may result in fetal death or morbidity due to erythroblastosis fetalis. From a genetic standpoint it is quite obvious that the contrasting obstetrical histories depend upon the homozygous or heterozygous nature of the *Rh* factor of the father's blood. The significant genetic crosses involved are given in Table IV.

That the *Rh* factor is inherited as a mendelian dominant chartcter was shown by Landsteiner and Wiener.[18] So far as the *Rh* factor is concerned, it is obvious that only infants heterozygous for the *Rh* factor (*Rhrh*) may acquire erythroblastosis or show any of the other evidences of this mother-fetus conflict.

The first one or two pregnancies with *Rh*+ fetuses in both sorts of matings may result in normal infants because a sufficient degree of isoimmunization has not yet been attained. But once the mother has been immunized all her future pregnancies with *Rh*+ fetuses will terminate in erythroblastosis fetalis. Since *Rh*— offspring cannot immunize the mother, it is obvious why only a few out of many pregnancies will result in affected infants in matings with a heterozygous father. In general, the incidence of erythroblastosis fetalis is higher in infants born in later pregnancies.

As already stated, erythroblastosis fetalis occurs but rarely, its incidence as given by Javert being but one in 438 full term deliveries. Undoubtedly this value will be somewhat greater if diagnostic *Rh* tests are applied in all cases of fetal and neonatal morbidity. In any event, the condition is not as frequent as we might expect when we consider that in 13 per cent of all random matings the father is *Rh*+ (85 per cent) and the mother is *Rh*— (15 per cent). Obviously, there are a number of factors of safety, the most important of which is the inability of many of these *Rh*— mothers to produce anti-*Rh* antibodies. Another important factor is the current tendency to small families, for even in matings which give clinical erythroblastosis in later pregnancies, the first one or two infants are frequently normal.

The evidence presented indicates that *Rh*+ fetal blood in one form or another enters the circulation of the *Rh*— mother. Since the *Rh* factor, in contrast to the blood factors *A* and *B*, is not present in body fluids (or other tissue cells) it must be the formed element itself i.e., the red blood cell or the stroma which finds its way into the maternal circulation. Whether or not this is possible without the presence of gross lesions in the placental circulation is as yet premature to decide. Assuming that such lesions are present,[12] their pathogenesis is of paramount importance. Theoretically such gross les-

TABLE IV. Heredity of Erythroblastosis Fetalis Depends on Heredity of the Rh factor.

1. *Rh* inherited as mendelian dominant
2. Dominant gene ..... *Rh*
   Recessive allele ..... *rh*
3. Three genotypes ..... Two phenotypes

RhRh ..... homozygous } ..... *Rh*+
Rhrh ..... heterozygous }
rhrh ..... recessive ..... *Rh*—

Significant Matings

Rh+ father × *Rh*— *mother*

Homozygous Father

Genotypes ..... *RhRh* × *rhrh*
Genes in Gametes ..... *Rh* *rh*
Offspring ..... *Rhrh*
(100% *Rh*+)

Every pregnancy may immunize Rh— mother:

Heterozygous Father

Genotypes ..... *Rhrh* × *rhrh*
Genes in Gametes ..... *Rh* *rh* ; *rh* ↓
Offspring ..... 50% *Rhrh*, 50% *rhrh*
(Half *Rh*+; half *Rh*—)

Rh— offspring cannot immunize *Rh*— mother.

ions may be due either to environmental conditions or else to constitutional defects in the mother. In any event, these lesions must recur and become operative in each succeeding pregnancy with an *Rh*+ fetus. However, one need not predicate the existence of gross lesions if it can be assumed that minute amounts of fetal blood acting over a long period suffice to induce an effective degree of isoimmunization. In that event, the question will arise whether or not this can occur under the physiologic conditions of pregnancy. Whatever the mechanism, the existence of anti-*Rh* agglutinins in the *Rh*— mothers is a fact which has been repeatedly demonstrated.

Once anti-*Rh* agglutinins have been produced, they pass readily through the placental barrier to act on the susceptible *Rh*+ fetal blood. There is no difficulty in accepting this view since it is generally recognized that maternal antibodies are the source of the passive immunity normally observed during the neonatal period.

Finally, the concept presented offers a suitable explanation for the markedly contrasting forms of erythroblastosis, namely the invariably fatal fetal hydrops on the one hand and the mild, frequently unrecognized anemia of the new-born on the other. Nothing is known at present as to how early in the course of pregnancy isoimmunization begins. However, there is indirect evidence that fetal hydrops results from a prolonged intra-uterine action of maternal anti-*Rh* agglutinins, while shorter periods of this activity produce the milder forms of icterus gravis or anemia.

Isoimmunization by *A* and *B* Factors and Early and Late Fetal Death

From a historical standpoint it is of considerable interest that more than 20 years ago incompatibility of the blood of the mother and fetus was held responsible for icterus neonatorum, icterus gravis and fetal death.[5, 8, 31] In some manner this incompatibility also adversely affected the birth weight. In this connection the terms homospecific and heterospecific pregnancies were employed by Hirszfeld and the only combinations considered by him to be compatible were those in which the blood groups of the mother and her infant were identical. Accordingly a mother of Group *A* or group *B* having an infant of group *O* was classified by him as a heterospecific pregnancy. Analysis of these early papers failed to reveal any reference to isoimmunization of the mother by the dominant blood factors *A* and *B* of the fetal blood. At that time the possibility of isoimmunization of the mother by dominant factors in the fetal blood was not recognized. This probably explained, at least in part, why the significence of these early observations was not appreciated.

Shortly after the pathogenesis of erythroblastosis fetalis was established, the writer had an opportunity to study the bloods of women having histories of abortions and stillbirths not attributable to erythroblastosis fetalis. It soon became evident that the *Rh* blood factor played only a comparatively minor role in these cases.[22] However, a difference was observed in the blood group of the mother on the one hand and of the father and of the fetus on the other, which could be interpreted as isoimmunition by the blood factors *A* and *B*. In these instances the mother's blood was lacking the blood factors *A* and *B*, one of which was present in the father and in the affected fetus. This sort of mating is defined as incompatible in contrast to those compatible matings in which the blood factors of the father and of the mother either are identical or in which the mother carries the dominant blood factor.

The two sorts of matings are classified in Table V.

TABLE V. Blood Group Matings.

Compatible		Incompatible
	♂ × ♀	
♂ × ♀	B × AB	♂ × ♀
0 × 0	AB × AB	A × 0
0 × A		B × 0
0 × B		A × B
A × A		B × A
B × B		AB × 0
0 × AB		AB × A
A × AB		AB × B

If we assume random mating between individuals of the four blood groups in the proportions found among the white population of the United States (O = 45 per cent, A = 41 per cent, B = 10 per cent and AB = 4 per cent), 65 per cent of all matings would be compatible and 35 per cent incompatible In a group of cases selected because of two or more instances of unexplained early or late fetal death it is significant that this ratio is altered so that there is a higher incidence of incompatible matings. This evidence along with other significant data is tabulated in Table VI.

It is noteworthy that in the matings of the *Rh*— mothers with erythroblastotic infants the incidence of incompatible blood group matings is even lower than normal. Furthermore, in the exceptional group, i.e., where the mother is *Rh*+, the incidence of incompatible matings is considerably higher than normal. Shortly after these observations were made on a smaller series, the author found Taussig's reference[35] to the significant findings of Paroli and Tranquilli-Leali which are also recorded in Table VI.

The values given by the Italian workers in terms of homospecific and heterospecific pregnancy do not correspond with the figures given in Table VI which were derived by the author from an analysis of their data in terms of the concept of isoimmunization.

Although the statistical data presented in Table VI are most suggestive and very likely significant, they are not as convincing as the studies in erythroblastosis fetalis. This is to be expected since the heterogenous group studied is not by any means as clearly defined a clinical entity as is erythroblastosis fetalis. There are obviously several factors responsible for fetal death in this group, but these preliminary studies strongly suggest that at least one of them will be found to be isoimmunization of the mother by the incompatible A or B blood of the fetus.

If we assume that isoimmunization by factors A and B is as likely to cause fetal death early in the pregnancy as later, we may lump the two series in order to indicate the varying distribution of the blood groups in the mothers, in the fathers, and in their sum, i.e., the parents (Table VII).

An unusually high incidence of group O in the mothers and an equally high incidence of group A in the fathers is evident. As is to be expected in a group of assumedly random matings the distribution in the parents does not differ much from the distribution in the general population.

Further proof for isoimmunization by fetal blood factors A and B can be obtained from a small number of cases in which specific increase of agglutinins can be demonstrated following an abortion or stillbirth. Two illustrating examples are given in Table VIII.

It is true that specific increase of agglutinins was at first not correlated with fetal death,[14, 21] but these observations were made in women following their first pregnancies. If the views presented are correct, these women should

TABLE VI. Isoimmunization by Factors *A* and *B*.

Matings	*Compatible*	*Incompatible*
Random	65%	35%
115 with two or more miscarriages	46	54
43 with two miscarriages or stillbirths	44	56
41 with fetal death*	41.5	58.5
215 Rh— mothers†	75	25
28 Rh+ mothers†	50	50

*Paroli[32] and Tranquilli-Leali.[36]
†Mothers of erythroblastotic infants.

Table VII. Blood Group Incidence.

Group	Random	158 Mothers	158 Fathers	316 Parents
O	45	50	28.4	39.2
A	41	33.5	51.9	42.7
B	10	13.9	14.6	14.2
AB	4	2.5	5.1	3.8

TABLE VIII. Specific Increase of Maternal Isoagglutinins.

Blood Group of Mother	*History*	*Titre*	*Blood Group of Husband*
0	4 Abortions	Anti-A 1:320	A
		Anti-B 1: 40	
0	1 stillbirth	Anti-A 1: 80	B
		Anti-B 1:640	

show a high incidence of abortions and stillbirths in their later pregnancies.

In contrast to the findings on erythroblastosis, intra-uterine hemolysis does not occur in this group in spite of specific increases of the normally present agglutinins, so that the actual cause of early or late fetal death is still to be established. There is, however, experimental evidence to indicate why these cases do not show manifestations of erythroblastosis fetalis. The significant fact is that in contrast to the *Rh* factor, the *A* and *B* blood factors are present not only in the red blood cells, but also in the tissue cells and body fluids of the fetus. However, this applies to more than 80 per cent of the cases (secretors), and in the remaining cases, described as non-secretors, the *A* and *B* blood factors may perhaps be limited to red blood cells.[25] Nevertheless, proof is still to be provided that this is the explanation for the high incidence of incompatible blood group matings in the small group of *Rh*+ mothers of erythroblastotic infants included in Table VI.

It is not known how early in the course of pregnancy isoimmunization begins. A very early onset may be assumed since red cells form in the yolk sack as early as the fourth week.[1] According to Kemp[15] and Moreau[30] agglutinable factors in the blood could be demonstrated in the fetus between the second and third month. From the point of view of the present discussion, the more fundamental property of antigenic (immunizing) function may be assumed to have an even earlier origin.

It is of interest to speculate why a higher incidence of early fetal death may result from isoimmunization by *A* and *B* factors than by the *Rh* factor. In the first place, the effects of isoimmunization by the *A* and *B* may occur earlier because anti-*A* and anti-*B* are normally present antibodies. Secondly, and this may prove to be far more significant, the specific reaction of maternal anti-*A* and anti-*B* with the excess of *A* and *B* factors in tissue cells may exert a far more lethal effect on the embryo or the fetus than the specific reaction of maternal anti-*Rh* on the fetal red blood cells exclusively. In the latter case, neither vital organs nor tissue cells can be affected because the *Rh* factor is limited to the red blood cells.

In 1925, Hirszfeld made the significant observation that the incidence of *A* children is lower in matings of father *A* × mother *O* than in the contrasting mating of father *O* × mother *A*. At one point in his paper he states that in the former mating this is probably due to loss of *A* offspring through miscarriages and stillbirths. It is very curious that this significant finding was soon neglected by Hirszfeld himself, probably because he finally accepted Bernstein's hypothesis that a group *O* mother can not have an *AB* child because of genetic reasons rather than because of Hirszfeld's earlier explanation, of heterospecific incompatibility.

Since Hirszfeld's observation on the selective loss of infants containing the dominant blood factor *A* seem to support the concept of isoimmunization by the factor *A*, seven additional heredity studies were analyzed by Levine. These results are presented in Table IX.

Accordingly, the results in six of the seven heredity studies confirm the concept of selective fetal death by isoimmunization. At this point mention may be made that in erythroblastosis fetalis there is also a selective effect on heterozygous *Rh*+ fetuses. These considerations suggest that further studies be carried out in which the obstetrical histories are recorded to take into account fetal death by miscarriage, stillbirth or neonatal death.

TABLE IX. Incidence of Group *A* Offspring in Matings *O* × *A* and *A* × *O*.

	Father × Mother *O* × *A*	Father × Mother *A* × *O*
Hirszfeld (15 authors)[8]	65.1	56.0
Hirszfeld and Hirszfeld[9]	63.1	60.5
Landsteiner and Levine[16]	60.6	44.8
Weiner and Vaisberg[38]	54.8	52.5
Clausen[2]	66.3	62.0
Vuori[37]	46.7	63.8
Landsteiner and Wiener[17]	68.4	25.0
Levine and Landsteiner[27]	77.1	45.2

As an example, the following family can be cited:

In Family F.C.B.

	Group	*Rh*
Mother	O	—
Father	A	+
1. Child M	O	+
2. Stillborn		
3. Child C	A	—
4. Stillborn		
5. Child L	O	—
6. Child K	O	—
7. Stillborn		

In this instance there are two incompatibilities, involving both the blood groups and the *Rh* factor. Of the four surviving children one has the dominant factor of the father, the remaining three have the recessive property of the mother. The question arises, what was the blood group or the *Rh* reaction in the stillbirths?

Other Evidence of Isoimmunization and Fetal Death

As already stated, erythroblastosis fetalis furnishes a thoroughly established precedent for the concept that genetic and constitutional factors may cause fetal death by isoimmunization. Thus the data on the *Rh* factor and erythroblastosis fetalis indirectly serve to support the view that the same mechanism induced by other blood factors may also cause fetal death. In general, the effects of isoimmunization by any fetal blood factors should have some familial trend and more specifically, its modus operandi in erythroblastosis fetalis is now well understood. Although there are not yet available similar data regarding fetal deaths induced by other blood factors, this may be implied from the recent and important statistical studies of Gardiner and Yerushalmy.[6,39] These workers observed that there is a familial tendency to stillbirths and neonatal deaths, and write as follows: "One may speculate that among other things, the father may also play an important part in these cases of repeated loss to the family." "It may therefore be indicated that the study of infant loss should embrace also factors in the father. This seems to be especially important in the cases of habitual abortions and in cases of families in which many infants have been lost through stillbirths and neonatal morbidity."

These significant observations indicate the necessity of correlating similar statistical investigations with serological blood studies. But even at this early stage it is already highly suggestive that the conclusions of Gardiner and Yerushalmy as well as the findings of Robinson and Corner on selective fetal death in animals are not incompatible with the concept of isoimmunization.

These investigators studied the causes of intra-uterine fetal deaths in pigs and ferrets, and infertility in horses. Robinson[33] and Corner[3] concluded that genetic and constitutional factors are probably responsible for a high incidence of fetal death. In the case of ferrets and pigs, these workers found normal fetuses alongside of dead macerated fetuses in a uterus which was free of detectable disease. Corner assumes the presence of genetic lethal factors analogous to those found in Drosophila and in the case of the yellow mouse studied by Cuenot, Castle and Little and Kirkham (cited by Corner[3]).

To make the analogy closer, it may be stated that selective fetal death is a characteristic manifestation of isoimmunization by the blood factors *Rh* and *A* and *B*. It is clear that only heterozygous *Rh*+ (*Rh rh*) fetuses or new-born can acquire erythroblastosis fetalis. More specifically, reference may be made to the F.C.B. family discussed above in which two out of four surviving children have the double recessive property of the mother (group *O*, *Rh*—). Furthermore, in the case of twins only one of whom had erythroblastosis fetalis, the affected member was *Rh*+, while the *Rh*— individual was normal.

Isoimmunization by blood factors in the fetus may or may not be entirely compatible with the concept of genetic lethal factors, but there is no reason to assume that isoimmunization by the fetus should be limited to man. On the other hand, there is serologic evidence to indicate that isoimmunization by pregnancy

should occur frequently in many animal species. It is a well established fact, based experimentally upon the isoimmunization resulting from repeated transfusions, that the individuality of blood in many species is greater than among humans. This phenomenon seems to occur more readily in animals than in man. Furthermore, pregnancy offers certain conditions which are peculiarly favorable to isoimmunization, i.e., slow administration of the antigen over a long period. This probably explains the general impression that the manifestations of isoimmunization by the *Rh* factor in fetal blood occur more frequently than isoimmunization in *Rh*— patients who are exposed to repeated transfusions with *Rh*+ blood.

It must be kept in mind that the data on the role of isoimmunization by the blood factors *A* and *B* in causing fetal death is only of preliminary nature. There are several criticisms which can readily be directed against this concept, one of which is the existence of the normally present isoagglutinins anti-*A* and anti-*B*. The very suggestive data offered here are extensive enough to warrant further investigation. Perhaps the simplest approach to the subject is a heredity study of selected families which show a high incidence of miscarriages, stillbirths and neonatal deaths.

Summary

It is now established that a specific disease of the fetus and the new-born, erythroblastosis fetalis, can be attributed not to disease in the father or in the mother, but rather to genetic and constitutional differences in the antigenic composition of their erythrocytes. The actual mechanism depends upon isoimmunization of the mother by the *Rh* factor in fetal blood and the intra-uterine action of maternal anti-*Rh* agglutinins on susceptible fetal blood. Evidence of a preliminary nature is presented to indicate that the same mechanism induced by other blood factors may be responsible for both early and late fetal death, i.e., abortions and stillbirths.

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TWINS AND SUPER-TWINS

GALTON and the nine-handed Armadillo started it. The former pointed out over half a century ago that identical twins offered a direct test of the interactions of heredity and environment in human development—*if*, as Galton assumed, identical twins did have exactly the same heredity. The Armadillo took a hand about 1909, when it challenged the curiosity of young biologists Newman and Patterson, newly arrived at the University of Texas. Their inquiries into the private reproductive customs of the armadillo showed how these creatures routinely have identical quadruplets, developed from a single fertilized egg. Galton's hunch, strengthened thus and in other ways, is now generally accepted, and we recognize identical twins as a duplicate set of human genes parading in two bodies.

Biologist Newman never quite got over his armadillo experience, and he has spent much of his life busily delving into the problem of human heredity as it is illuminated by twins. His persistent search for identical twins reared apart has yielded more of such pairs than anyone else has ever succeeded in finding and testing—twenty in all. The readers of this JOURNAL are well acquainted with Harold and Holden, and with Twin "A" who was reared in Canada and identical "O" reared in London, to mention only two.

Since his armadillo days Professor Newman has written a multitude of articles and four books about twins, human and otherwise: *The Biology of Twins* (1917), *The Physiology of Twinning* (1923); *Twins: Heredity and Environment* (in cooperation with Psychologist Freeman and Statistician Holtzinger, 1938). The present volume* is a popular summary mainly of Newman's studies on twins and the higher multuplets, which he calls "super-twins."

It is extensive rather than exhaustive, with a goodly sprinkling of popular folklore about twins, some of which Newman re-tells with a doubtful "for what it is worth." He makes an odd error in discussing Thornton Wilder's fascinating psychological study of Esteban and Manuel in the *Bridge of San Luis Rey:* "His Esteban and Manuel so resented their twinship that they hated each other. This attitude is well known to exist occasionally between one-egg twins, but far more normal and common is their outstanding affection." The whole point of Wilder's story was that so great was the love of these two for each other that they are inseparable even in the face of so perplexing a problem of falling in love with the same girl. The death of one leaves the other only half a person until the fall of the bridge ends that tragic separation. Newman points out that Wilder himself is a twin, but he neglects to say whether identical or fraternal.

About a third of the book is devoted to the Dionne quintuplets and other multuplets. While the quints are sure-fire popular interest material, they have yet to add greatly to the sum of heredity-environment knowledge. No undoubted cases of a sextuplet birth has come to Dr. Newman's attention. The six instances listed in the medical literature have about them certain elements of

(*Concluded on page* 96)

**Multiple Human Births* by Horatio Hackett Newman, Professor of Zoology, University of Chicago. Pp. xii-214 illustrated. $2.50. Doubleday Doran Company, Inc. New York: 1940.

AN UNUSUAL CASE OF TWINNING IN JERSEY CATTLE*

F. W. Atkeson, Franklin Eldridge and H. C. Fryer†

FERTILITY PHENOMENON

These Jersey cows, full sisters, and born less than a year apart, are both bisex twins, and both fertile. Considering the rarity of twins in cattle, and the high incidence of freemartin-sterility in females of bovine bisex twins, this occurrence is so unlikely as to suggest strongly that it has a genetic explanation rather than being due merely to chance.

TWO cows, full sisters, born less than a year apart, each twin with a bull, and each fertile is a rare occurrence. These two cows were registered Jerseys and were excellent specimens of the breed. The older of the two sisters has calved five times in five years and 15 days, and had one set of twin bulls. The younger sister has calved four times in four years and 31 days, with no twins. Both breeding records are remarkably regular.

The regulations of the American Jersey Cattle Club require the breeder to record the fact when twins are born and the sex of each calf must be indicated, even though only one is registered. Most cattlemen consider that females born twin with a male are so frequently freemartin and so rarely fertile that it is uneconomical to raise them to breeding age. Upon investigation, it was found that cow *A*, dam of the above-mentioned cows, had calved 13 times, thrice giving birth to twins, for a total of 16 offspring —an exceptionally large number for a cow.

Reports are highly variable concerning the incidence of twinning in cattle. Estimates in percentage of total births range from 0.35 per cent to 2.94 per cent[1]; the majority of the estimates being between 1.3 to 2.0 per cent. It is commonly accepted that the tendency toward twinning is hereditary since several reports, including those of Lush[6]

*Contribution No. 151 from the Department of Dairy Husbandry, Kansas Agricultural Experiment Station.

†The authors acknowledge their indebtedness to George Cooper, Manager of Ralph L. Smith Farms, Chillicothe, Mo., and C. J. Frayer, Manager of The Oaklands Jersey Farm, Ann Arbor, Mich., for breeding records used in this study.

and Hewitt[3] have shown that any abnormal percentage of twins in a population can be traced usually to one or two families. Neither the mode of inheritance of this tendency nor the percentage of multiple births among the progeny of a "twinning" cow have been determined. The probability, therefore, for any certain cow to have twins can be determined only as the percentage of that animal's offspring that were twins. Since cow *A* calved 13 times, 3 of the times giving birth to twins, the best estimate of the probability for any one birth to result in twins would be the fraction 3/13.

Independent of the event of having twins there is the event of having bisexual twins. Since the percentage of monozygotic twins in cattle is negligibly small, (Belic[1] reporting the largest estimate, five per cent, and Lillie[5] stating that they were rarely if ever found) the ratio of twin males to bisexual twins to twin females would be 1:2:1. Having twins, therefore, the probability of having bisexual twins would be the fraction 1/2.

Nothing is known of the inheritance of fertility in a female bovine born twin to a male. The occurrence of fertility in twins of this sort, however, has been accepted as 13 per cent by Lillie,[5] 8 per cent by Koch[4] and 10 per cent by Dukes.[2] The average of these estimates is approximately 10 per cent, hence the fraction 1/10 is the best estimate of the probability of the female being fertile in each birth of bisexual twins. If the null hypothesis is set up that neither the heredity nor the innate physiology of Cow *A* would cause her to be any more likely than any other "twinning" cow to produce a fertile female in a bisexual pair, the probability that any particular birth of Cow *A* would be bisexual twins in which the female was fertile is $(3/13) \cdot (1/2) \cdot (1/10) = 3/260$. This event has occurred twice in thirteen pregnancies. Hence, by the binominal probability function the probability of this event is—

$$P = \frac{13!}{2!\ 11!} \cdot (3/260)^2\ (257/260)^{11} = .009.$$

This means, then, that if heredity is not a factor, only about 9 times in 1,000 such observations would the phenomena discussed above occur. This probability is so small that the validity of the null hypothesis is doubtful. It strongly suggests the possibility that the fertility of a heifer twin to a male may be controlled by heredity.

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Bovine Sweepstakes Winners?

While the arithmetic of figuring the probability that the above two cows could have occurred cannot be quarreled with, the author's assumptions may be questioned. One important factor omitted in essaying the situation is the sampling error. The chaps who win one sweepstakes prize get their names in the papers, but those who win twice in ten trials get their pictures in too. The fact that the mother of these two heifers (who are far more personable than even the average one-time sweepstakes winner) turned so neat a reproductive trick does not guarantee that in thirteen more pregnancies she would repeat the performance. The ever-present tendency for unusual situations to be brought to public attention and thus to get into the record is well known to all who analyze human genetics pedigrees.

Another factor which may complicate the situation is that in addition to knowing nothing about the inheritance of a tendency for a heifer born twin to a bull to be fertile, really very little is known about the proportion of such heifers who are in fact free martins. Because of the widespread belief that such heifers are usually sterile, few are raised to an age when the matter can be tested.

These quibbles and others which might be cited detract not at all from the interest of this unusual occurrence. We hear stories of almost mythical cows who have six or eight sets of twins, all of whom lived. If any such reproductive counterparts of Paul Bunyan's fabulous ox actually exists, the Journal of Heredity would like to hear of them, preferably with photographs!—Editor.

CHILDLESSNESS: VOLUNTARY OR INVOLUNTARY?

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OF thirty million wives in the United States, five million will leave no offspring. How many of these five million wives were childless against their will? How do the proportions of voluntary and involuntary childlessness differ in various regions, in various social and economic groups, in various races? What part of voluntary childlessness is due to insistence of wife, what to the husband? Why, in general, do married persons try to avoid having children; why *do* they[1] have children? Such questions are fundamental to the implementation of eugenic policy, and they have received much less attention than they deserve.

Some years ago I asked more than 100 mature adult students in my classes at University College, University of Southern California, to contribute information as to childless couples known to them so well that they felt no doubt as to the reason for childlessness. Of the 862 childless marriages thus tabulated, 65 per cent were classed as voluntary and 33 per cent as involuntary. I pointed out[4] that these couples "were nearly all from the educated part of the population, with an excess of professional people, particularly teachers." They were certainly not representative of the whole American population.

Utilizing family records collected in New York City during a health survey Clyde V. Kiser tabulated data on 564 marriages, of which 159 were represented by replies to questionnaires, the remainder by data secured in personal interviews.[2] Among these were 291 women who reported that they had never been pregnant. Although the sample was small, it seemed to be fairly representative of the population of New York City. More than 40 per cent were foreign born. Nothing is said of religious affiliations, although this is important in the motivation of childbearing. A large part of the foreign-born population of New York City is either Jewish or Roman Catholic, and these two religious groups are probably better represented in Dr. Kiser's sample than in my first study or in the second study of 3,013 marriages here presented. In neither of my own studies is there any information as to religious affiliation.

Over three-fourths of the "never pregnant" women in Dr. Kiser's study reported that neither they nor their husbands had ever done anything since marriage to prevent conception, and Dr. Kiser noted cautiously that "absence of conception among couples married 10 years or more is in large part an involuntary situation."

"However prevalent may be the practice of contraception for the purpose of postponing and spacing pregnancies," he remarked as a "tentative conclusion," "such practices can not be held responsible for any major share of existing permanent childlessness."

The questions involved are important enough to demand much larger samples than the few hundred contributed from New York City in Dr. Kiser's study and the few more hundred in my earlier report. Moreover, it seems obvious that the percentage of involuntary childlessness would vary with the educational, economic, and social levels of the families concerned. In order to attack the problem from another side, I therefore collected information as to childless couples classified on the Minnesota Occupational Rating Scale, as reported in Table I.

These data were provided by several hundred students in classes in family

relations which I have taught at the University of Southern California and in summer sessions at the Colorado State College of Agriculture (Fort Collins) and the Colorado State College of Education (Greeley). Most of these students were mature adults representing many different states although mainly from the Middle West and Far West. They were instructed to take only unbroken marriages known to them so intimately that they felt sure of the facts, and only marriages which had never had children and never would have children, either because of the age of the wife or for other reasons such as disability (e. g., sterilization) of one parent. No one person knows the facts as to many marriages, but most persons know, among their own circle of near relatives and close friends, at least a few marriages on which they can report quite as factually as could the husband or wife directly involved.

The involuntarily childless wives in this study can not be called "never pregnant." Doubtless some of them had had stillbirths or miscarriages, although no living children. It is doubtful whether any large group of married women can be called "never pregnant," since there are many spontaneous abortions of fertilized ova which occur so soon after conception that the woman does not know she was pregnant—thinking, at most, that she had a delayed menstruation. Physiologically it would be desirable to know how many married women are actually never pregnant; eugenically it is only surviving children that count.

The percentages in Table I are about what most readers would probably expect. The educated part of the population would for many obvious reasons be likely to practice contraception more widely and successfully than the uneducated. Without attaching too much importance to conclusions based on relatively small numbers, one can draw some interesting inferences from these figures. The group classed as "rural owners" seems to have the smallest amount of voluntary sterility. Farmers are generally recognized to be more "family-minded" than other parts of the population and it is not surprising that a childless home, among them, is usually undesired.

The high proportion of voluntary sterility in Class V, composed of semi-skilled, minor clerical, and minor business, will not surprise those who have followed recent studies of differential fertility. A generation or two ago the professional class was most likely to practice contraception, and to limit the size of family sharply because of economic and social pressure. During the past generation the business class has tended to follow suit and even to pass its predecessor. Analysis of data from the 1910 census showed[5] the fertility of the business group to be lower than that of the professional group, and a similar tendency is found in the data of the 1935-36 National Health Survey, analyzed elsewhere[3] by C. V. Kiser. The lower-income group of white collar workers are—or at least have been during the past 15 or 20 years—under particular economic pressure. The attempt to survive during the depression and to raise the standard of living seems to

TABLE I. Motivation of Childless Marriages.

	Voluntary		*Involv.*	*Total*	*CR*
I. Professional class	504	57%	391	895	4.5
II. Semi-professional and managerial	310	55%	256	566	3.5
III. Clerical, skilled trades, and retail business	350	54%	301	651	3.3
IV. Rural owners	115	42%	159	274	
V. Semi-skilled, minor clerical, and minor business	184	57%	138	322	3.8
VI. Slightly skilled	79	47%	89	168	1.0
VII. Unskilled rural and urban	63	46%	74	137	0.8
Totals	1605	53%	1408	3013	

have led not merely to low fertility but to an unusual amount of complete and voluntary sterility.

To determine the statistical validity of the percentages of voluntary childlessness I calculated the Critical Ratio of the difference from that of rural owners, and this ratio is given in the last column of Table I. Unfortunately the differences in percentage of voluntary sterility in the two lowest socio-economic groups are not enough to permit conclusion as to statistical validity. All the other Critical Ratios are well over 3.0 and therefore technically significant.

So far as they go, the 3,013 completed marriages in this study indicate that about one-half of all the childlessness in the Mountain and Pacific Coast states at the present time is voluntary. Whether or not the couples were physiologically capable of having children, they did not want a family and are satisfied with their sterility.

The figures confirm the general observation that farm owners are more family-minded than any other large group in the United States. They also bear out the conclusion reached in other studies, that the small-business and clerical group now tends to replace the professional group as the one most likely to forego parenthood, presumably in the hope of improving its competitive position in the economic and social scale of city life.

Beyond this, the table at least gives no evidence that motivation differs very greatly in the ranks of unskilled labor in the West.

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THE LIVING AND THE DEAD

THIS is a $12.50 book* and deserves a $12.50 review. It contains 554 figures scattered through 1116 pages, 19 of which are given to an index, and two plates of a splash of milk. There is an uncounted number of references of adequate format. Many minor and most of the major prophets will find their work and ideas cited, though the omission of W. E. Castle, Ales Hrdlicka, H. S. Burr, Paul Weiss, and Wm. Seifriz from the constellation is passing strange in view of their contributions to some part of the field covered by the volume. The type gives comfortable reading and the book is well bound. It weighs 3.19 pounds and is published by the Cambridge University Press and The Macmillan Company. So much for its mechanical aspects.

The context may be considered under four headings: viz. The purpose; the factual data; the meaning read into the data; and the adequacy of that meaning for interpretation of the Growth-Form interdependence. The purpose is to show how the growth of living things and the forms they present may be interpreted in terms of physical principles and expressed by mathematical formulae.

The factual data are encyclopedic in range and their detail is reminiscent of Fraser's *Golden Bough*. The organisms used for development of the thesis range alphabetically from Acanthocystis to the Zeuglodon; and the entire galaxy of physical principles is invoked, save possibly electricity and magnetism. Gravity, temperature, light, osmosis, surface energy are all given their due niche. The mathematical exposition of ponderal growth is compact and sufficient; while

**On Growth and Form:* by Sir D'Arcy Wentworth Thompson. Pp. 1116. $12.50. Macmillan Co. 1943.

that of spiral increment in shells and other organisms has an elegance which excites admiration as much for the material as for the treatment. Outside of these and the comparison of related forms via projections, the analysis is more verbal than figured. The stuff out of which the book is built is solid. The demonstration of how growth and form may be factored by physical forces, and how mathematical formulae may be fitted to growth and form leaves little to the imagination. Within these limits the ground-work is here.

The Meanings

So far so good. But the meaning read into the factual data is another matter. In his exaltation of physical principles to pre-eminence as the chief if not the only determinants of growth and form, the author becomes vulnerable on several fronts. His argument is weakened by the unrestrained use of analogy; by its *post hoc ergo propter hoc* character; by its dependence upon the mathematics of engineering; by its scant recognition of other factors and forces; by its exclusiveness; and by its failure to utilize the Paretan principle of interdependence. Special pleading and begging the question are used when inconsistencies become too glaring. In other words the cards are stacked for the plaintiff, and as in any other frame-up, contrary evidence is inadmissible.

The inference that the form of *Campanularian calycles* is determined by the same forces which produce a similar form in a splash of milk is just one example of the type of analogy used. And the conclusion that because surface tension gradients are exhibited as daughter cells acquire individuality, surface tension is the primary factor in cell increase in number, is a *post hoc* reasoning which neglects the fact that surface tension is the product, not the producer of the specific chemical reactions which yield two cells where but one existed before. Now the utility of the mathematics of engineering in evaluation of rates, dimensions, and contours is unquestioned. But such complete dependence upon mathematics leads as here to exclusion of important material, an overweighting of certain aspects, and inevitably to one-sided conclusions; not to mention the pernicious habit of trying to force data into pre-conceived formulae.

Furthermore, there are aspects of growth and the forms it produces which are not amenable to such procedures. The progressive specialization of cell substance as the cells of the developing organism undergo successive divisions is one of them. Some other system such as the Woodgerian must be used to map the complete story. I suspect that the cell knows little of calculus and cares less; that while it may construct geometric figures for the amusement of case-hardened mechanists, it is mostly concerned in getting along the best it can in the place God has put it, and with carrying on the duties incident to that place. The fact that man has had to devise such tools as the Standard Deviation, the Probable Error, and the Coefficient of Variability in order to encase cell activities within the mathematical cage might possibly mean that living things tend to exhibit a certain degree of free enterprise, or at least that they are not completely regimented by one set of influences.

And this brings us to the really serious defect in Thompson's argument: namely that he ignores as inconsequential the part played in growth and in sculpturing the forms it produces by chemical and genetic forces. Such exclusiveness gives just basis for the derisive attitude of Charles Fort towards the self-sanctified claims to omniscience put forward by many tillers of the scientific field.

The chemical nature of the substance produced by growth is just as much a factor limiting the course of growth and the forms this substance can take as is any physical principle or combination thereof. The chemical properties of bone, chitin, and cellulose determine their distinctive participation in growth and form quite as much as do the physical forces of gravity, temperature, light, or surface energy. And subtending all

this is the directive force of genetics. Neither temperature, light, gravity, surface energy, osmosis, electricity nor magnetism determine the difference between the right hand and the left; or that the big toe shall always be different from the little. These do not determine that the growth and form of an elephant shall always be different from that of a giraffe. Nor do they determine the persistence of species-specific characteristics of growth and form in the face of the countless variations in absolute and relative intensity of the impinging physical forces.

What Thompson seems to miss entirely is that growth and form are the product of sets of interdependent forces of which the physical are but one component. True it is we do not know what the genetic force is; the same is the case with electricity, gravity, surface tension, and the rest. And just as the existence of the latter is known, accepted, and distinguished by the effects produced by each; so is the existence of a genetic force known, and perforce accepted by its distinguishing effects. And the same holds true of chemical energy. And if mathematical representation of effect is to be taken as the criterion of existence, then genetic force is established on just as true though not as extensive a foundation as is physics or chemistry.

It is clear from all this that the meaning read by Thompson into his factual data is inadequate to interpret the interdependence of growth and form. For this interdependence is compounded of at least three elements: direction, substance, and state of substance. The last, which is the domain of physics, derives from the nature of the second, which is the domain of chemistry. This in turn is subtended by the first, which is genetics.

Because of this this reviewer feels towards this book much as the inhabitants of Poictiesme must have felt when they came to examine closely the monument to Manuel their hero on his silver stallion. The monument is impressive as an historical document. Like the pyramids it is solid and lasting. But like the pyramids it is the tomb of a dynasty which is dead. The King is dead. Long live the King!

FREDERICK S. HAMMETT.

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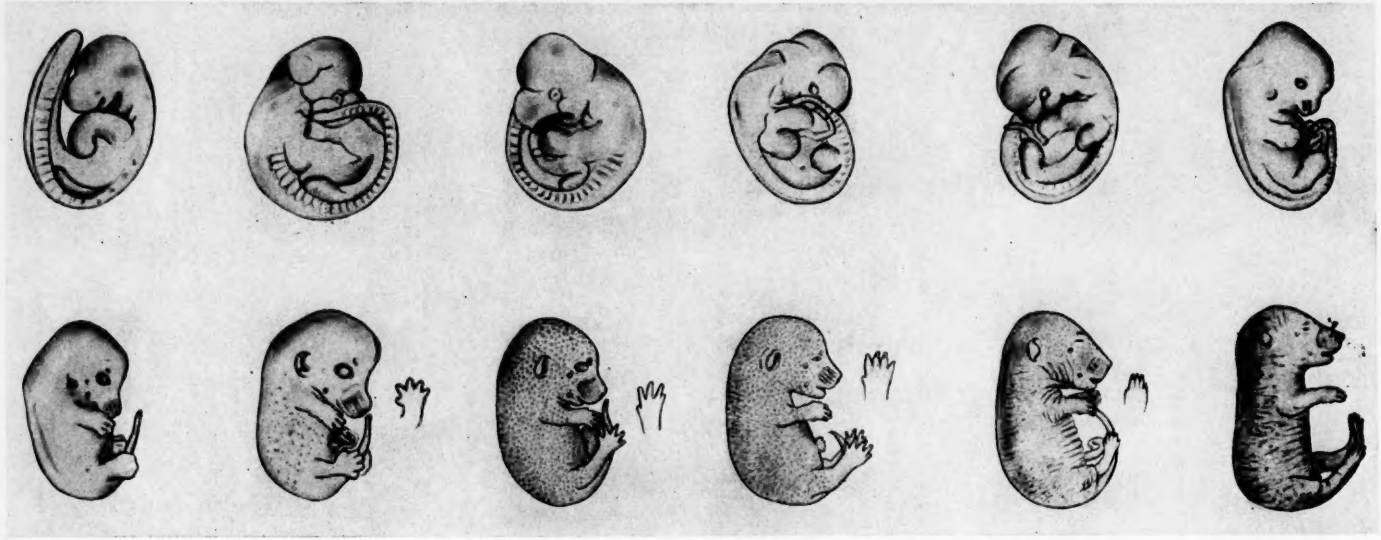
Mode of Operation of the Rough-Hair Gene

A study was made of the origin and early development of the hair follicles in guinea pigs, both smooth-coated and rough, through observations of sections, of entire embryos, and of whole mounts of the skin. The first primordia (exclusive of those of vibrissae) appear in embryos of about 19-mm. crown-rump length as measured after fixation, and of about 27 days copulation age. Arising in orderly sequence in definite regions of the skin, they have spread over most of the surface of the embryo by the 30-mm. stage (age about 32 days).

In the normal smooth-coated guinea pig the follicles point in general away from regions that appear to be growing rapidly at the time of origin of the primordia. The formed hairs point in the opposite direction. It is probable that these active regions (posterior end, distal ends of limbs and ears) are the highs of physiological gradients which may serve as orpanizers of polarity in the follicles by stimulating unequal growth on the opposite side of the primordia. Under this hypothesis the hereditary irregularities in hair direction (whorls, featherings, crests, etc.) are caused by genetic factors which locally alter the primitive metabolic relationships and set up new gradients in particular regions.—COLIN, EDWARD, *Jour. Morph.*, March, 1943.



DEVELOPMENT OF MOUSE EMBRYOS

Figure 3

The important "landmarks" which may be used to time the age of embryos are here shown. For details see text, pages 89 to 92.

THE DEVELOPMENT OF SOME EXTERNAL FEATURES IN MOUSE EMBRYOS

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IN work on the development of mutant characters in the mouse, it is necessary to know the age of the embryos. The observation of vaginal plugs is the standard method for the timing of pregnancies. This method is somewhat tedious, however, and there are numerous instances in the literature where authors, instead of specifying the age, have recorded the crown-rump length of their embryos. Not knowing the age of their material, they evidently hoped that the linear measurement would eventually be translated into age by subsequent workers. So far as I am aware, there is only a single paper, by Chang,[1] which gives some data on the relation of embryonic age to length. That paper is published in a rather inaccessible journal and shows considerable overlapping between the length distributions of subsequent days. According to Chang, an embryo of 5.5 mm. crown-rump length, for instance, might be anything from nine to twelve days old, and similar though smaller uncertainties of timing by this criterion are found in later stages of gestation.

For a variety of reasons, the crown-rump length of an embryo is a poor guide to its age. In the very gelatinous embryos of nine to about eleven days, artificial deformations occur very easily. When such embryos are dissected out of their membranes in an unfixed condition, they tend to shoot out of their compartment like a jack-in-the-box, and in doing so they usually recoil and become unduly stretched. They commonly fail to return to their normal shape when transferred into saline or a fixative; this has evidently happened to Chang's nine- and ten-day stages, which are much too long. On the other hand, if embryos of eleven or twelve days are first fixed *in utero*, contraction of the amnion apparently sometimes forces the embryo into a slightly cramped position, in which it then becomes fixed. Feeble active movements occur occasionally in 15-day embryos; from the 16th day onwards these movements become stronger, and notably in 17- and 18-day old foetuses a good deal of wriggling occurs when they are dropped into the fixative. As a consequence, some of them become fixed in unduly stretched or otherwise abnormal postures, which render the measurement of length both difficult and inaccurate. Apart from these artifacts, there is of course some genuine variation in embryonic length. Finally, as is well known to every worker, there commonly occur embryos which are more or less retarded in development, and which are much smaller than the rest of the litter.

The object of this paper is to draw attention to the fact that, from the stage of development of certain external features, mouse embryos from nine to 18 days of age can be timed with perfect confidence to within 24 hours. The facts are no doubt familiar to many workers, but they do not seem to have been published in a readily accessible form. For the sake of completeness the crown-rump lengths will also be given, though their value is only limited.

The material used for this study was collected in May, 1942. Two strains of mice were used, the "mixed strain" and an albino strain. The former was extremely heterogeneous; the latter probably less so, as it had been very mildly inbred. Heterogeneous material was used in preference to pure lines, as a

*The author is indebted to Dr. J. C. Mottram for the mice used in this study. Grateful acknowledgments are due to Mrs. Margret Simons for the beautiful illustrations.

sample of undiminished embryonic variability was desired. The two strains showed no differences relevant for our purposes and are treated together below. The pregnancies were timed as follows: Males were put into the cages with virgin females at nine o'clock in the evening (British Double Summer Time) and removed again at nine o'clock next morning. Pregnant females were subsequently picked out and dissected between ten and eleven o'clock in the morning. The time difference from day to day is thus 24 hours to within a fraction of an hour. The time of gestation was counted from the removal of the male from the cage. Any litter is thus at least one hour older than its nominal age (if mating occurred immediately before the removal of the male, and if the female was killed at ten o'clock); in an extreme case it may be 14 hours older than the nominal age (if mating occurred immediately the male was put in the cage with the females, and if the female in question was killed at eleven o'clock). According to Snell *et alii,* mating happens most frequently during the first half of the night. Taking account of the time shift due to the double summer time, it seems reasonable to assume that on an average the litters will be older than their nominal age by about eight hours or one third of a day.

Embryos of nine to eleven days were fixed (Bouin's fluid) *in utero* to avoid the "jack-in-the-box" effect and later dissected out; 12-day embryos were dissected under saline and then transferred into Bouin; 13- to 18-day old embryos were dissected without immersion in saline. Up to, and including, the 16-day stage Bouin penetrates the embryonic skin without difficulty. In most 17-day and all 18-day embryos the keratinization of the skin presents a barrier to penetration, necessitating the removal of some of the skin.

Embryos up to the age of 15 days were measured to the nearest half of a millimeter; thereafter the sources of error mentioned above do not justify a greater accuracy of measurement than to the nearest millimeter. The data are given in Table I. It will be seen that the mean crown-rump length increases steadily with age in an almost linear fashion. Since the range of lengths of successive days overlaps in many cases, the age determination of a single embryo by length alone would often leave the choice between two days. The matter is somewhat improved if mean lengths of whole litters are compared. This will usually be possible in actual work, where one is rarely faced with the task of timing a single embryo. In the literature, unfortunately, the length of a single embryo has often been recorded rather than the average for the litter. Data about the mean length of whole litters are given in Table II. The figures in brackets give the number of young in each litter, and an italicized numeral indicates that the litter contained in addition one obviously retarded young, which has not been included in the mean value. There is much less overlapping between succes-

TABLE I. Measurements of Mouse Embryos

Age (days)	Number of embryos	Number of litters	Mean Length (mm)	Range (mm)
9	18	3	1.9	1.5 — 2.5
10	25 (4)	4	3.7	3.0 — 4.0
11	38 (1)	4	5.9	5.0 — 7.0
12	25	4	7.5	7.0 — 8.5
13	22	3	8.8	8.0 — 9.5
14	23	3	10.5	10.0 — 11.5
15	29 (1)	4	12.7	11.0 — 13.5
16	21 (1)	4	15.0	13.0 — 16.0
17	26	4	16.7	14.0 — 19.0
18	34	4	19.8	18.0 — 22.0
Total	261 (7)	37		

NOTE: Figures in brackets denote retarded embryos, the length of which has not been utilized in calculating the mean length of the group.

sive days now, but the smallest 12-day litter comes practically within the 13-day range, and one 17-day litter falls within the 16-day range. Thus even the timing of whole litters by their mean crown-rump length would lead to occasional errors. Hence, though the length of the embryos will be of value in timing a litter, additional criteria of age are desirable.

We shall therefore proceed to describe the development of some external features. We do not aim at giving a complete description of everything that is visible in the embryos. Only those structures will be pointed out which are easily visible in fixed embryos under the dissecting microscope, and which change sufficiently rapidly from day to day to be useful in estimating the age of the embryos. The age determination from the ninth to the 17th day of gestation could be based on the development of the limbs alone; a number of other features will, however, also be considered. The following description is to be regarded as a legend to the accompanying chart. The most useful features acquired since the previous day have been italicized.

Ninth Day

(9-1/3 days old, and so throughout)

At this stage the embryo is bent double, so that its somewhat swollen posterior end is lying close to the head; for this reason the length measurement is not strictly a "crown-rump" length. The anterior end is formed by the telencephalon; there are not yet any nasal processes, nor is there an olfactory pit. Mandibular and hyoid processes are well developed. The eye-cup is visible through the epidermis, but it does not yet noticeably bulge the surface. Ear vesicles are visible on either side of the rhombencephalon. A ridge, from which the limb buds will originate, is present laterally; the anterior limb bud forms a longish swelling of this ridge, but there is not yet any trace of a posterior limb bud. The tail has not yet started budding. The somites are clearly visible throughout most of the length, but do not yet reach the posterior end of the embryo.

Tenth Day

Widely separated medial and lateral nasal processes enclose a large and deep oval olfactory pit. The eye forms a small ill-defined bulge, at the hight of which the *lens vesicle* is visible. The first and second visceral clefts are still open throughout their lengths. The auditory vesicles are still visible. *The anterior limb buds form clearly defined semicircular rudders,* in which no separate footplate can be recognized yet; *the posterior limb buds form low longish swellings* of the ridge, which is very marked throughout its length. Somites are clearly defined throughout the whole length of the embryo, including the *short tail bud,* which contains about six to eight somites.

Eleventh Day

Medial and lateral nasal processes are in close contact and enclose a *narrow slit-like olfactory pit.* The eye is now clearly defined; *a ring of pigment surrounds its pupil* (except in albinos, and presumably in pink-eyed and pallid animals). The auditory vesicles are no longer visible. The first visceral cleft is closed (or about to be closed) ventrally to form the external auditory meatus; there is not yet any noticeable development of a pinna, though the six low tubercles, which are to form it, are discernible. *The naso-maxillary fissure is clearly visible throughout its length. A footplate has differentiated in the anterior limb buds,* while the *rudder-like posterior limb buds* are not yet clearly divided into leg and foot; the ridge connecting anterior and posterior buds is less distinct. The somites are now indistinct anteriorly, but still sharply defined in the posterior half, including the tail, which has grown in length considerably.

Twelfth Day

The naso-maxillary fissure is closed. There are rudiments of *three rows of sinus hairs (whiskers),* with three to four hair follicles each; there are also the faint beginnings of one sinus hair follicle over the eye and sometimes one on the cheek between eye and ear. The external auditory meatus is slit-like and

TABLE II. Mean Lengths of Litters of Mouse Embryos.

Age Days	General Mean (mm)	Mean Lengths of Individual Litters; Litter Size in Brackets.							
9	1.9	2.2	(6)	2.1	(6)	1.6	(6)		
10	3.7	3.8	(9)	3.9	(6)	3.6	(5)	3.3	(5)
11	5.9	5.9	(10)	6.5	(10)	5.9	(9)	5.2	(9)
12	7.5	7.4	(9)	7.4	(8)	7.3	(6)	8.3	(2)
13	8.8	9.0	(9)	8.5	(7)	9.0	(6)		
14	10.5	10.6	(8)	10.4	(8)	10.7	(7)		
15	12.7	12.0	(10)	12.4	(8)	12.6	(6)	13.0	(5)
16	15.0	15.3	(9)	15.0	(4)	14.5	(4)	15.0	(4)
17	16.7	18.0	(7)	17.0	(7)	15.1	(7)	16.8	(5)
18	19.8	19.5	(10)	19.6	(9)	19.8	(9)	20.8	(6)

there is not yet any distinct pinna. *The anterior footplate shows the faintest suggestion of fingers on its surface,* but is not yet appreciably indented on its margins; the posterior footplate is still smooth on its surface and perfectly circular in outline. Distinct segmentation is confined to the tail, though indistinct somites are still present all along the back. A small physiological umbilical hernia is present, but difficult to see on account of the crouched posture of the embryos.

Thirteenth Day

There are now *five rows of whiskers* with five to seven hair follicles in each. The *external auditory meatus is roundish;* there is now a *pinna, which forms a crest at right angles to the head,* without in any way covering the meatus. The *anterior footplate is clearly indented,* while the *indentations of the posterior footplate are still shallow.* Segmentation marked in distal part of tail, indistinct on lower third of back. Umbilical hernia marked.

Fourteenth Day

The free margin of the pinna is turned forward forming a flap which covers about 1/3 of the external auditory meatus. The fingers on the front legs are separate distally, but still webbed proximally; the posterior footplates are deeply indented. Hair follicles have appeared on the body, but few or none on head and along the middle of the back. Segmentation has disappeared from the tail. Umbilical hernia marked.

Fifteenth Day

The flap of the pinna covers about 2/3 of the external auditory meatus. Fingers and toes separate throughout, without webbing, and very divergent. The end-phalanges of the fingers begin to show. *Hair follicles now also on middle of back and on the head, except on the eye-lids, which surround the eyes like smooth spectacles.* Slight transverse wrinkling of the skin on the flanks. Umbilical hernia obvious.

Sixteenth Day

Flap of pinna covers external auditory meatus completely and in most cases is already attached anteriorly. In 15 out of 21 embryos the eye-lids leave a more or less narrow segment of the eye uncovered; in two or three instances the eye was nearly as wide open as on the previous day; in the remaining six cases the palpebral fissure was closed. The end-phalanges are clearly visible in fingers and toes. *Fingers 2-5 are now nearly parallel to each other and joined by skin proximally, but not near the tips. The toes are somewhat more divergent and separate for a greater length. The umbilical hernia has disappeared.* Wrinkling of skin more extensive, now also on legs, neck, and under the chin. Tips of whiskers sometimes visible.

Seventeenth Day

Fingers and toes completely joined together as in the newborn mouse. Eye-lids closed (one out of 26 foetuses had one eye wide open, presumably a pathological feature). Wrinkling of skin still more marked; on the flanks the transverse folds are now much more conspicuous than the goose-flesh pattern of the hair follicles, but on face and head the follicle pattern is still very marked. Short whiskers erupted.

Eighteenth Day

The hair follicles, notably those on head and face, have become flat and inconspicuous; *the head, which looked prickly the day before, is now essentially smooth,* with some very fine skin wrinkling delimiting irregularly diamond-shaped areas, in which some flattened hair follicles can still be made out. Whiskers longer.

Even without the help of length measurements, the features described above make it easy to time mouse embryos to within 24 hours; in the earlier stages, up to about 15 days, interpolation should allow estimations to within 12 hours. However, in work where greater accuracy is required, the vaginal plug method will remain superior.

A word should be said about the retarded embryos. These are not only much smaller, but also correspondingly less developed than their normal litter mates. The developmental difference may amount to 24 hours or more. In some cases there was evidence that the embryos were already dead, or moribund. As there are many factors which may retard development, but hardly any which could accelerate development beyond the normal rate, it seems a justifiable procedure to disregard these obviously pathological specimens.

Summary

Crown-rump length measurements of mouse embryos from 9-1/3 to 18-1/3 days of age are given; these allow a rough, but not quite reliable estimation of embryonic age. The development of various external features provides criteria for the determination of the age to within 24 hours, and slightly more accurately in the earlier stages.

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CONCERNING THE INHERITANCE OF RED HAIR

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ALTHOUGH there is little doubt of the hereditary nature of red hair color, the details of the transmission of this trait remain somewhat obscure. It is generally agreed that the factors responsible for black hair are epistatic to those determining red. Even in dark brown haired individuals the detection of red pigment may be difficult. These facts, together with the probable existence of modifiers of the depth of red pigmentation, complicate the study of the inheritance of red hair color. Nevertheless, two main hypotheses have been advanced:

1. The presence of red pigmentation in the hair depends on a dominant factor, *R*, which is inherited independently of the factors determining black or brown hair color (Fischer,[4,5] Davenport and Davenport[3]). (However, C. B. Davenport, in a letter to Saller published in part by the latter,[8] writes that since the publication of his original paper he has collected much additional data and that "usually the red hair acts like a recessive trait but there seem to be many exceptions.")

2. The production of red pigment depends on homozygosity for a recessive factor (Philiptschenko and Liepin, 1925, quoted from Saller,[8] Saller.[7,8])

Conitzer,[2] in an extensive treatment and review of this subject, has concluded that the bulk of the evidence favors the first hypothesis, and this viewpoint seems to have gained rather general acceptance.[1,9]

Now, it is obvious that a decision as to which scheme is more nearly correct can most readily be reached through an analysis of the offspring of marriages involving two red headed people. On the second hypothesis, only red headed children should result from such a union, while on the first there should result something under 25 per cent of non-red headed offspring, with the exact proportion depending on the frequency of the gene in the population. Reports concerning the children of marriages between red heads are rare, only seven published ones being known to the author. The results of these former reports are summarized in Table I. From this it is obvious only that further data are needed.

Recently I have had the privilege of going through the files of the Genetics Record Office, Carnegie Institution of Washington, at Cold Spring Harbor, L. I., N. Y., and have been able to locate 26 additional reports of fertile marriages between two red headed individuals. It should perhaps be emphasized that the pedigrees have for the most part been sent in to the Record Office by interested people scattered all over the country, so that standardized criteria of redness and investigation of cases by trained investigtors have not been possible. Some of these pedigrees probably constitute part of the "additional data" which Davenport referred to in his letter to Saller quoted above. The results of these marriages are summarized in Table II. Among 114 offspring of such unions, 101 were red heads and 13 had hair of some other color. It is unfortunate that in most cases there are no data on the exact hair color of the non-reds. Careful examination of the hair of the non-reds and verification of parentage where possible would have been highly desirable. Be that as it may, if we take the data at face value, the occurrence of so many non-red heads would seem to exclude the hypothesis of simple recessiveness, without, however, necessarily proving hypothesis 1 as stated above. If the factor for red hair is completely dominant, one would expect to find more than 13 non-red headed children among these 114 offspring. This follows from an analysis of gene frequencies.

The proportions of the various hair types in the United States are roughly

as follows (Gould, 1869, quoted from Conitzer,[2] Trotter[10]):

brown and darker (in which red pigmentation would be detected with difficulty or not at all by the untrained observer)	0.575
dark blond and lighter (in which red could usually be detected with no difficulty)	0.400
red	0.025

The proportion of red headed people in the latter two categories, which are the only ones in which the inheritance of red hair can be studied, is 0.059. Assuming, with the first hypothesis, that red is completely dominant, the frequency of the "non-red factor," *r*, is $\sqrt{1.000 - 0.059}$, or 0.97, and of the dominant *R*, 0.03. The frequency of the genotypes *RR*, *Rr*, and *rr*, assuming random mating, is thus approximately 0.001, 0.058, and 0.941. Among the red heads the proportion of *RR* is 0.017, and of *Rr* 0.938, i.e., the heterozygous class is much more common, as is always the case when a rather infrequent factor is involved. Matings between two red heads will be of the following types, with the results noted below.*

For the matings described in Table II the expectation is thus 86.5 red heads and 27.5 non-reds. χ^2 for the difference between observation and expectation is 10.09, which with one degree of freedom has a *P* value much less than 0.01. There is a very real deficiency of non-red headed offspring among the children of these marriages, on the basis of the hypothesis of dominance.

At least two alternate hypotheses concerning the inheritance of the trait appear feasible. One is that the *R* gene is an incomplete recessive which is occasionally penetrant in the heterozygote. A high proportion of the red heads in the population would thus be the homozygous type. Perhaps the heterozygotes tend to be the "sandy reds," in contrast to the clear red homozygote. The other hypothesis is that the red color of the hair is under the control of either of two different factor pairs. If both of the assumed factors are recessive, then when two red haired people, in whom the genetic basis of the trait differs, marry, they should have some or all non-red headed offspring, depending on their heterozygosity or lack of the alternate factor. Unless one of the two factors is considerably rarer than the other, a high proportion of the marriages might be expected to result in all non-red offspring. Actually, this occurs only once among the 26 marriages, and this in a "family" of one child. If the trait may be due to either a dominant or a recessive factor, then the dominant must be much rarer than the recessive, since otherwise again a higher proportion of marriages between reds would yield non-red headed children.

While a critical decision between these possibilities is not feasible, a further consideration of the data lends some support to the first. If we assume that red hair is the result of a nominally recessive factor which is occasionally pene-

TABLE I. A summary of the offspring of previously reported marriages between two red headed people.

Marriage no.	Total no. of children	No. with red hair	No. without red hair	Investigator
1	3	3	0	Davenport and Davenport (1909)
2	9	0	9	" " *
3	4	1+2?	1?	Rodenwaldt (1927), quoted from Saller (1931)†
4	1	0	1	Saller (1927)
5	2	2	0	Saller (1931)
6	3	3	0	" "
7	5	5	0	Keers (1932)

*In the light of available data this must be considered an extremely unusual result. Four of the children had *black* hair; one, brown; three, golden; and one, yellow. The parents had dark red hair.

†One of the children was certainly red haired, two reputedly so, and the reports concerning the fourth were conflicting.

*Mating	Frequency	Offspring RR	RR′	R′R′
$RR \times RR$	0.88^2	0.7744		
$RR \times RR'$	$2 \times 0.88 \times 0.12$	0.1056	0.1056	
$RR' \times RR'$	0.12^2	0.0036	0.0072	0.0036
		0.8836	0.1128	0.0036

trant in the heterozygote, then the results of Table II could be accounted for by the further assumption that some two per cent of the individuals heterozygous for the red factor possessed red hair. Thus, if we let p equal the frequency of the non-red factor, now designated as R', and q the frequency of R, then on the assumption of a two per cent penetrance of the erstwhile dominant R, the proportion of non-red headed people among blondes, 0.941, equals $p^2 + 1.96\ pq$, and the proportion of red heads, 0.059, equals $q^2 + 0.04\ pq$. The solution of either of these two equations gives a p value of 0.773 and a q value of 0.227. Among phenotypic red heads, 0.88 are homozygotes and 0.12 heterozygotes. Random mating would result in the following types of offspring:*

Of the RR' individuals, 0.1105 will be non-red headed, and 0.0023 red headed. The phenotypic ratio will thus be 0.8859 red heads to 0.1141 non-red heads, or, in terms of 114 children, 100.99:13.01. It is worth emphasizing that when an uncommon recessive factor is involved, even a low penetrance in the heterozygous condition will lead to many exceptions to the recessive rule.

On this assumption of a two per cent penetrance of the factor for red hair when heterozygous, 77 per cent of the marriages between red heads should result in all red headed children. Actually, in the 26 families studied, 69.3±8.6 per cent of the marriages yielded all red heads. If we exclude family 26, for reasons given in the table, the percentage is 72.0±9.0. Moreover, in those marriages between a red head and a non-red head or between two non-red heads which yield red headed offspring, there should be a slight excess of red heads over expectation on the hypothesis of complete recessiveness. The data of Saller[8] suggest that this is the case. However, among the marriages yielding non-red headed children, the proportion of non-reds should be 0.505, whereas actually, excluding family 26, it is 0.343± 0.080.

Summary

From an analysis of the results of 26 marriages between two red headed people, it appears probable that the color of the hair is not determined by a single

TABLE II. A summary of the offspring of marriages between two red headed people as recorded at the Eugenics Record Office.

Marriage no.	Total no. of children	No. with red hair	No. without red hair
1	13	13	0
2	4	4	0
3	5	3	2
4	1	1	0
5	6	4	2
6	2	2	0
7	7	7	0
8	7	7	0
9	3	2	1
10	6	3	3*
11	4	4	0
12	1	1	0
13	1	1	0
14	4	4	0
15	5	5	0
16	1	1	0
17	3	3	0
18	1	1	0
19	6	6	0
20	3	3	0
21	1	0	1
22	4	3	1
23	1	1	0
24	5	5	0
25	10	8	2
26	10	9	1†
	114	101	13

*The three non-reds were black haired. This could be a rare case of incomplete epistasis of black over red in the parents and some of the offspring.

†The parents had auburn hair. The first nine children had red hair, whil ethe tenth had brown or black. The latter might have been a young child at the time of the report, in whom detectable red pigment had not yet developed.

*Type	Frequency	Offspring RR	Rr	rr
$RR \times RR$	0.017^2	0.000289		
$RR \times Rr$	$2 \times 0.017 \times 0.983$	0.016711	0.016711	
$Rr \times Rr$	0.983^2	0.241572	0.483145	0.241572
		0.758428		0.241572

completely dominant or recessive factor. Rather, the data are consistent with the hypothesis that the characteristic is dependent upon a single incompletely recessive factor, hypostatic to the factors determining black or dark brown hair color. However, the possibility that all red headedness does not have the same genetic basis and that there are at least two different factors involved cannot be excluded.

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TWINS AND SUPER-TWINS

(*Continued from page* 80)

doubt, and it seems fairly certain that no sextuplets were ever born alive. Among the 60 cases of quintuplets in the literature, some 47 are considered to be authentic. During the past one-and-a-half centuries, four sets have been born in the United States, in 1776, 1800, 1896 and 1936. The 1896 set was born in Kentucky: they lived for some three weeks. With modern baby incubators and the newer nutritional knowledge they might have survived as did the Dionnes. Without either Dr. Dafoe or the necessary machinery, their doom was certain.

Methods of diagnosing one-egg and two-egg twins are discussed at length. The test by the eye alone, whether the twins can be told apart, is probably the best single criterion, with finger and palm prints next. The human eye is able to differentiate an amazing number of human physiognomies, all patterned along remarkably similar lines. The very fact that the eye encounters any difficulty in telling two people apart is strong evidence that a large number of facial features have been integrated, and that no significant differences have been noted. Thus there is good statistical basis for giving the eye an important place as a diagnostic tool. Combined with other elements, such as the blood groups, finger prints, mirror imaging, etc., few pairs offer any difficulties of classification.

A chapter on twins and human heredity discusses the importance of twins in giving us an insight into the interactions of heredity and environment. The reviewer found this chapter the least satisfactory. The point that twins can be successfully used as an assay of the limits of environmental modification of a great variety of human characteristics perhaps needs more emphasis than it received. This is brought out excellently in citing the contributions twins have made to our knowledge of diseases both mental and physical. The use of twins in the study of mental disease is still only beginning, but already it has considerable promise. The statewide study of twins with tuberculosis and with psychoses now being made by Kallman and others is beginning to bear very promising fruit. It might well have been noted by the author.

The book closes with a review of the twenty cases of identical twins reared apart which were the basis of Dr. Newman's earlier book. The lay reader will get much fascinating information from this unusual book, but he will not get a complete account of research on twins in this and other countries.—R. C.

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